3 Scale-Up and Postapproval Changes for Nonsterile Semisolid Dosage Forms: Manufacturing Equipment

I. INTRODUCTION

Any equipment changes should be validated in accordance with current good manufacturing practices (CGMPs). The resulting data will be subject to examination by field investigators during routine GMP inspections. The information here is presented in broad categories of unit operation (particle size reduction or separation, mixing, emulsification, deaeration, transfer, and packaging).

Under scale-up and postapproval changes (semisolid) (SUPAC-SS), equipment within the same class and subclass are considered to have the same design and operating principle. For example, a change from a planetary mixer from manufacturer A to another planetary mixer from manufacturer B would not represent a change in design or operating principle and would be considered the same.

A change from equipment in one class to equipment in a different class would usually be considered a change in design and operating principle. For example, a change from a planetary mixer to a dispersator mixer demonstrates a change in operating principle from low-shear convection mixing to high-shear convection mixing. These types of equipment would be considered different under SUPAC-SS.

Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class but different subclasses. In many situations, these changes in equipment would be considered similar. For example, in Section III, Mixing, under the convection mixers, low shear, a change from an impeller mixer (subclass) to a planetary mixer (subclass) represents a change within a class and between subclasses. Provided the manufacturing process with the new equipment is validated, this change would likely not need a Changes Being Effected (CBE) Supplement. At the time of such a change the applicant should have available the scientific data and rationale used to make this determination. It is up to the applicant to determine the filing category.

II. PARTICLE SIZE REDUCTION AND SEPARATION

A. Definitions

1. Unit Operations

a. Particle Size Reduction

Particle size reduction is the mechanical process of breaking particles into smaller pieces via one or more size-reduction mechanisms. The mechanical process used is generally referred to as milling.

i. Particle

A particle is either a discrete crystal or a grouping of crystals, generally known as an agglomerate.

ii. Particle Size Reduction Mechanisms

- Impact—Particle size reduction caused by applying an instantaneous force perpendicular to the particle or agglomerate surface; the force can result from particle-to-particle or particle-to-mill surface collision
- Attrition—Particle size reduction by applying force parallel to the particle surface
- Compression—Particle size reduction by applying a force slowly (as compared with impact) to the particle surface toward the center of the particle
- Cutting—Particle size reduction by applying a shearing force to a material

b. Particle Separation

Particle separation is particle size classification according to particle size alone.

2. Operating Principles

a. Fluid Energy Milling

Fluid energy milling is particle size reduction by high-speed particle-to-particle impact or attrition (also known as micronizing).

b. Impact Milling

Particle size reduction by high-speed mechanical impact or impact with other particles (also known as milling, pulverizing, or comminuting) is known as impact milling.

c. Cutting

Cutting is particle size reduction by mechanical shearing.

d. Compression Milling

Particle size reduction by compression stress and shear between two surfaces is known as compression milling.

e. Screening

Particle size reduction by mechanically induced attrition through a screen (commonly referred to as milling or deagglomeration) is called screening.

f. Tumble Milling

Tumble milling is particle size reduction by attrition, using grinding media.

g. Separating

Particle segregation based on size alone, without any significant particle size reduction (commonly referred to as screening or bolting), is also known as separating.

B. Equipment Classifications

1. Fluid Energy Mills

Fluid energy mill subclasses have no moving parts and primarily differ in the configuration or shape of their chambers, nozzles, and classifiers.

- Fixed target
- Fluidized bed
- Loop or oval
- Moving target
- Opposed jet
- Opposed jet with dynamic classifier
- Tangential jet

2. Impact Mills

Impact mill subclasses primarily differ in the configuration of the grinding heads, chamber grinding liners (if any), and classifiers.

- Cage
- Hammer air swept
- Hammer conventional
- Pin or disc

3. Cutting Mills

Although cutting mills can differ in whether the knives are movable or fixed, and in classifier configuration, no cutting mill subclasses have been identified.

4. Compression Mills

Although compression mills, also known as roller mills, can differ in whether one or both surfaces move, no compression mill subclasses have been identified.

5. Screening Mills

Screening mill subclasses primarily differ in the rotating element.

- Oscillating bar
- Rotating impeller
- Rotating screen

6. Tumbling Mills

Tumbling mill subclasses primarily differ in the grinding media used and whether the mill is vibrated.

- Ball media
- Rod media
- Vibrating

7. Separators

Separator subclasses primarily differ in the mechanical means used to induce particle movement.

- Centrifugal
- Vibratory or shaker

Please note that if a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to affect particle size or separation.

III. MIXING

A. Definitions

1. Unit Operation

Mixing is the reorientation of particles relative to one another to achieve uniformity or randomness. This process can include wetting of solids by a liquid phase, dispersion of discrete particles, or deagglomeration into a continuous phase. Heating and cooling via indirect conduction may be used in this operation to facilitate phase mixing or stabilization.

2. Operating Principles

a. Convection Mixing, Low Shear

Convection mixing, low shear, is a mixing process with a repeated pattern of cycling material from top to bottom in which dispersion occurs under low power per unit mass through rotating low shear forces.

b. Convection Mixing, High Shear

Convection mixing, high shear, is a mixing process with a repeated pattern of cycling material from top to bottom in which dispersion occurs under high power per unit mass through rotating high shear forces.

c. Roller Mixing (Milling)

Also known as milling, roller mixing is a mixing process by high mechanical shearing action where compression stress is achieved by passing material between a series of rotating rolls. This is commonly referred to as compression or roller milling.

d. Static Mixing

In static mixing, material passes through a tube with stationary baffles. The mixer is generally used in conjunction with an in-line pump.

B. Equipment Classification

1. Convection Mixers, Low Shear

This group of mixers normally operates under low shear conditions and is broken down by impeller design and movement. Design can also include a jacketed vessel to facilitate heat transfer.

- Anchor or sweepgate
- Impeller
- Planetary

2. Convection Mixers, High Shear

These mixers normally operate only under high-shear conditions. Subclasses are differentiated by how the high shear is introduced into the material, such as by a dispersator with serrated blades or homogenizer with rotor stator.

- Dispersator
- Rotor stator

3. Roller Mixers (Mills)

No roller mixer subclasses have been identified.

4. Static Mixers

No static mixer subclasses have been identified.

Please note that if a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to mix materials.

5. Low-Shear Emulsifiers

Although low-shear emulsification equipment (mechanical stirrers or impellers) can differ in the type of fluid flow imparted to the mixture (axial-flow propeller or radial-flow turbines), no subclasses have been defined.

IV. TRANSFER

A. Definitions

1. Unit Operation

Transfer is the controlled movement or transfer of materials from one location to another.

2. Operating Principles

a. Passive

Passive transfer is the movement of materials across a nonmechanically induced pressure gradient, usually through a conduit or pipe.

b. Active

The movement of materials across a mechanically induced pressure gradient, usually through conduit or pipe, is known as active transfer.

B. Equipment Classification

1. Low Shear

Equipment used for active or passive material transfer, with a low degree of induced shear, is classified as "low-shear" equipment:

- Diaphragm
- Gravity
- Peristaltic
- Piston
- Pneumatic
- Rotating lobe
- Screw or helical screw

2. High Shear

Active or mechanical material transfer with a high degree of induced shear is performed by what is known as "high-shear" equipment:

- Centrifugal or turbine
- Piston
- Rotating gear

A single piece of equipment can be placed in either a low- or high-shear class, depending on its operating parameters. If a single piece of equipment is capable of performing multiple discrete unit operations, the unit has been evaluated solely for its ability to transfer materials.

V. PACKAGING

A. Definitions

1. Unit Operation

a. Holding

The process of storing product after completion of manufacturing process and before filling final primary packs is known as holding.

b. Transfer

Transfer is the process of relocating bulk finished product from holding to filling equipment using pipe, hose, pumps, or other associated components.

c. Filling

Filling is the delivery of target weight or volume of bulk finished product to primary pack containers.

d. Sealing

A device or process for closing or sealing primary pack containers, known collectively as sealing, follows the filling process.

2. Operating Principles

a. Holding

The storage of liquid, semisolids, or product materials in a vessel that may or may not have temperature control or agitation is called holding.

b. Transfer

The controlled movement or transfer of materials from one location to another is known as transfer.

c. Filling

Filling operating principles involve several associated subprinciples. The primary package can be precleaned to remove particulates or other materials by the use of ionized air, vacuum, or inversion. A holding vessel equipped with an auger, gravity, or pressure material feeding system should be used. The vessel may or may not be able to control temperature or agitation. Actual filling of the dosage form into primary containers can involve a metering system based on an auger, gear, orifice, peristaltic, or piston pump. A head-space blanketing system can also be used.

d. Sealing

Primary packages can be sealed using a variety of methods, including conducted heat and electromagnetic (induction or microwave) or mechanical manipulation (crimping or torquing).

B. Equipment Classification

1. Holders

Although holding vessels can differ in their geometry and ability to control temperature or agitation, their primary differences are based on how materials are fed. Feeding devices include the following:

- Auger
- Gravity
- Pneumatic (nitrogen, air, etc.)

2. Fillers

The primary differences in filling equipment are based on how materials are metered. Different varieties of filling equipment include the following:

- Auger
- Gear pump
- Orifice
- Peristaltic pump
- Piston

3. Sealers

The differences in primary container sealing are based on how energy is transferred or applied. Energy transfer can be accomplished via the following:

- Heat
- Induction
- Microwave
- Mechanical or crimping
- Torque